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Medical Management Options for Hepatocellular Carcinoma

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1. Introduction

Hepatocellular carcinoma (HCC) is typically diagnosed late in the course of patients with chronic liver disease and cirrhosis. Hepatic reserve of the patient, as indicated by the Barcelona Clinic or Child-Pugh staging system, can be helpful in determining therapeutic options. Because of rapidly evolving new treatment options and varying availability of therapeutic approaches to individual patients attempts in generating algorithmic approaches for the treatment of patients with hepatocellular carcinoma may not be applicable to all situations. General treatment options can be divided into surgical or non-surgical approaches. Non-surgical approaches may be liver directed (such as transarterial chemoembolozation, percutaneous ethanol injection, radiofrequency ablation) or sysytemic therapy. Systemic palliative therapy of HCC has not been used routinely for a number of reasons; First, due to high rate of expression of drug resistance genes, including p-glycoprotein, glutathione-S-transferase, heat shock proteins, and mutations in p53, HCC has been considered a relatively chemotherapy-refractory tumor. Second, systemic chemotherapy has been difficult to be tolerated by patients with significant underlying hepatic dysfunction and may have less efficacy in patients with significant cirrhosis. Third, clinical investigations of chemotherapy in advanced HCC have been undertaken in diverse patient populations (Asian versus North American/European) making the interpretation of the results difficult for the overall population. Recently there has been a resurgence of interest and enthusiasm for systemic therapy of HCC with the emergence of data showing benefit from several targeted therapies.

This chapter will focus on the non-surgical systemic treatment of HCC which includes chemotherapy, immunotherapy, molecularly targeted therapy, hormonal therapy, Immunomodulatory/antiangiogenic therapy and ongoing clinical trials of new targeted agents.

2. Chemotherapy/immunotherapy

2.1 Single agent regimens

2.1.1 Antracyclines

Although there is no approved treatment for HCC in the United States, the European Union, or elsewhere in the world, doxorubicin has been commonly used as a first-line chemotherapy treatment for this disease. First approved by the US Food and Drug Administration in 1974 for breast cancer, doxorubicin has been the subject of multiple clinical trials in HCC. Early encouraging response rates as high as 79% of doxorubicin single agent (Olweny et al.,1975) has not been supported by later studies. Most studies have reported an objective response rate around 20 percent with doxorubicin doses of 75 mg/$m^{2.}$ Despite the modest objective response rate one clinical trial involving 106 patients has shown that doxorubicin had a small survival advantage compared to best supportive care alone (median survival 10.6 versus 7.5 weeks)(Lai et al.,1988) While the clinical trials that occurred from 1977 to 1990 performed in HCC with doxorubicin as a single agent at doses ranging from 40 to 75 mg/m2 demonstrated a survival range from 3.0 to 4.1 months, (Ihde et al., 1977; Johnson et al.,1978; Falkson et al., 1984a; Falkson et al., 1984b; Colombo et al.,1985; Melia et al.,1987; Kalayci C et al., 1990) a more recent trial comparing single agent doxorubicin to nolatrexed showed a median survival of 32 versus 22 weeks in favor of doxorubicin (Gish et al.,2007). The higher than expected survival in both treatment groups might be due to advances in the management of patients with HCC including better supportive therapies, such as growth factors and greater expertise in the treatment of patients with cirrhosis. A limited number of phase III studies note higher response rates but no survival benefit with doxorubicin monotherapy compared to non-oxaliplatin 5-FU-based regimens and single agent etoposide (Choi et al.,1984; Falkson et al., 1978; Melia et al.,1983).

Both epirubicin and mitoxantrone have an approximately similar level of antitumor efficacy as doxorubicin (response rates 10 to 25 percent) (Pohl et al.,2001; Dunk et al.,1985). In contrast, the single agent activity of pegylated liposomal doxorubicin (PLD) is limited (Lind et al., 2007).

2.1.2 Fluoropyrimidines

Although there is extensive hepatic metabolism, 5-Fluorouracil (5-FU) has been utilized in the treatment of HCC with acceptable low toxicity and efficacy. Adequate doses have been able to be administered in the setting of hepatic dysfunction or jaundice. Response rates with 5-FU monotherapy have been low. However, when given in combination with leucovorin, response rates as high as 28 percent have been reported (Porta et al., 1995).

While single agent treatment with the oral fluoropyrimidine capecitabine (Patt et al., 2004) has shown an encouraging 25% response rate in one small study, a lower objective response rate (three partial responses among 50 treated patients) was noted in a subsequent larger phase II study evaluating the same dose of capecitabine in combination with oxaliplatin (Bogie et al., 2007).

2.2 Interferon alfa immunotherapy

Although interferon alfa has shown activity in preclinical models against HCC, several clinical trials have shown inconclusive results. An early Chinese randomized trial of 75

patients suggested superior response rates and better tolerability of interferon alfa compared to single agent doxorubicin (Lai et al., 1989). In another randomized trial, 75 patients with inoperable HCC were randomly assigned to receive interferon alfa 50 mU/m² intramuscularly three times weekly or best supportive care. Reported median survival was significantly improved in the interferon group (14.5 versus 7.5 weeks) with an objective response rate of 31 percent. Treatment was well tolerated with fatigue being the most common side effect requiring a dose reduction in only 34 percent of patients (Lai et al., 1993). On the contrary in a second trial utilizing a much lower dose of interferon alfa 3 mU three times weekly for one year versus symptomatic treatment only 6.6 percent of patients achieved a partial response with no survival benefit (Llovet et al., 2000).

Other chemotherapy and immunotherapy single agents with reported modest activity (mostly partial response and/or disease stabilization in HCC include irinotecan, gemcitabine and thalidomide (O`Reilly et al., 2002; Yang et al. et al., 2000; Lin et al., 2005).

2.3 Combination chemotherapy and immunotherapy regimens

2.3.1 Folfox

In an Asian trial of 371 patients with advanced or metastatic HCC modified FOLFOX-4 was directly compared to single agent doxorubicin (50 mg/m² every three weeks) the median survival in the FOLFOX arm, was 6.5 versus 4.9 months, p = .00425. FOLFOX was associated with better median PFS, objective response rate, and disease control rate, 53 versus 33 percent. Although the FOLFOX group had higher sensory neuropathy, most cases were mild, and there were no significant differences in the rate of grade 3 or 4 toxicities(Qin et al., 2010).

2.3.2 Xelox

Bogie et al. evaluated capecitabine (1000 mg/m² twice daily for 14 of every 21 days) in combination with oxaliplatin (130 mg/m² every three weeks), there were only three partial responses among 50 treated patients (objective response rate 6 percent) Stable disease in 29 patients led to a disease control rate of 72 percent. Median overall and progression-free survival was 9.3 and 4.1 months, respectively (Bogie et al. 2007).

2.3.3 Gemox

In a phase II study involving 32 cirrhotic patients with previously untreated advanced HCC, gemcitabine (1000 mg/m² by fixed dose rate infusion) on day 1 was followed by oxaliplatin (100 mg/m²) on day 2, with both drugs repeated every two weeks. The objective response rate was 18 percent, and an additional 58 percent had disease stabilization. Median survival was 11.5 months. Treatment seemed to be more effective in patients with nonalcoholic rather than alcoholic cirrhosis (Louafi et al., 2007).

2.4 Gemcitabine plus pegylated liposomal doxorubicin

In a phase II trial, 41 patients were treated with gemcitabine (1000 mg/m² days 1 and 8) plus pegylated liposomal doxorubicin (30 mg/m² on day 1) every 28 days. There were three complete and seven partial responses (overall response rate 24 percent), the median TTP was 5.8 months, and median overall survival was 22.5 months. Treatment was well

tolerated, with grade 3 to 4 toxicity limited to neutropenia (17 percent) and thrombocytopenia (2 percent) (Lombardi et al. 2011).

2.5 Gemcitabine and cisplatin

Parikh et al. evaluated the combination of gemcitabine (1250 mg/m^2 on days 1 and 8) and cisplatin (70 mg/m^2 on day 1 of every 21-day cycle) was associated with an overall response rate of 20 percent (Parikh et al., 2005). Grade 3 to 4 toxicities included anemia (37 percent), neutropenia (13 percent), thrombocytopenia (7 percent), transaminitis and mucositis (3 percent each). A second trial using a slightly different dosing regimen (cisplatin 25 mg/m^2 on days 1 and 8, gemcitabine 1000 mg/m^2 on days 1 and 8) reported a more favorable toxicity profile but a lower response rate (one partial response among 15 patients (Chia et al., 2008).

Other combination regimens include cisplatin plus doxorubicin with response rates 18 to 49 percent (Lee et al., 2004; Czauderna et al., 2002), cisplatin, mitoxantrone, and continuous infusion 5-FU with objective response rates 24 to 27 percent in two different studies (Yang et al., 2004; Ikeda et al., 2005), cisplatin, epirubicin and infusional 5-FU with a response rate 15 percent (Boucher et al., 2002;) cisplatin, doxorubicin plus capecitabine with a response rate of 24 percent (Park et al., 2006).

2.6 Combination of chemotherapy with interferon-alfa

2.6.1 The PIAF regimen

The immunomodulatory cytokine interferon alfa has been utilized in combination with different chemotherapy drugs in the treatment of HCC. One of the most aggressive combinations of this drug involves cisplatin, interferon alfa and infusional 5-FU, the so called PIAF regimen. Leung et al. evaluated this combination in 50 advanced stage HCC patients and found an objective response rate of 26 percent. Overall median survival of the entire population was nine months and eight of the resected patients remained in complete remission from eight to 26 months. Toxicity was mainly myelosupression and mucositis with no treatment related deaths (Leung et al., 1999). In another trial 188 unselected patients with chemotherapy-naive unresectable HCC were randomly assigned to doxorubicin monotherapy (60 mg/m^2 every three weeks) versus PIAF (cisplatin 20 mg/m^2 on days 1 through 4, interferon alfa 5 MU/m^2 subcutaneously on days 1 through 4, doxorubicin 40 mg/m^2 on day 1, and 5-FU 400 mg/m^2 on days 1 through 4) (Yeo et al., 2005). Objective response rates and median survival favored the PIAF regimen but the difference did not reach statistical significance. Toxicity was more in the PIAF arm, with more pronounced myelosupression and hypokalemia (Yeo et al.,2005).

Although the role of PIAF regimen in the treatment of HCC remains unclear, it may be considered for patients with a good performance status and liver function.

2.6.2 5-FU plus interferon alfa

Patt et al. evaluated 43 patients with advanced HCC on a regimen of infusional 5-FU (200 mg/m2 daily for 21 of 28 days) plus interferon alfa (4 mU/m2 three times weekly and found an objective response rate of 33 percent(Patt et al.,2003 (Patt et al., 2003). Two of four patients with HCC who were subsequently resected had a complete histologic response.

Despite the presence of cirrhosis in 71 percent of the patients with HCC, toxicity was moderate, with grade 3 or 4 stomatitis, fatigue, and hematologic toxicity in 33, 5, and 9 percent of patients, respectively. A similar level of benefit (objective response rates between 33 and 50 percent, one-third to one-half complete) has been seen with combinations of systemic interferon alfa with intrahepatic arterial 5-FU in patients with advanced HCC and major portal vein thrombus (a contraindication to transhepatic arterial chemoembolization) (Sakon et al., 2002; Ota et al., 2005; Nagano et al. 2007). A weekly bolus regimen of 5-FU 750 mg/m2 plus interferon alfa 9 MU three times weekly however, was much more toxic and ineffective in a small series of 10 patients with no sustainable responses (Stuart et al., 1996).

3. Molecularly targeted therapy

Existing evidence points to the possible role of epidermal growth factor receptor (EGFR)/EGF (HER1) signaling pathway in the carcinogenesis of HCC (Huether et al.,2005; Hung et al., 1993; Yamaguchi et al., 1995; Myaki et al., 2000; Schiffer et al.., 2005; Hopfner et al., 2004; Wu et al., 2003; Ito et al., 2001; Thomas et al., 2005). These data have led to the clinical trials evaluating the role of biologics such as erlotinib and cetuximab in HCC patients. HCCs are highly vascular tumors with high levels of expression of vascular endothelial growth factor (VEGF), thus suggesting a possible therapeutic role for agents targeting VEGF and/or the VEGF receptor (VEGFR). Similarly the Raf/MAP kinase pathway has been implicated in HCC tumorigenesis (Huynh et al.,2003) with a potential therapeutic role for drugs that inhibit Raf kinase pathway. There is a constant research to find less toxic more active targeted treatments in this disease.

3.1 Sorafenib

Efficacy of sorafenib, an oral small molecule tyrosine kinase inhibitor, was first noted on a phase I trial (Liu I et al., 2006; Strumberg D. et al., 2005). Further studies did not suggest a high level of objective tumor shrinkage but provided stable disease (Abou-Alfa GK et al., 2006). Eventually SHARP trial confirmed a survival benefit compared to best supportive care alone. SHARP trial randomly assigned 602 patients with inoperable HCC and Child-Pugh A cirrhosis to sorafenib (400 mg twice daily) versus placebo (Llovet et al., 2008). Overall survival, the primary endpoint, was significantly longer in the sorafenib-treated patients (10.7 versus 7.9 months), as was time to radiologic progression (5.5versus2.8months). Treatment was well tolerated with manageable side effects. These results established sorafenib monotherapy as the new reference standard systemic treatment for advanced HCC. In another trial 226 Asian patients with Child-Pugh A cirrhosis and no prior systemic therapy for HCC received sorafenib 400 mg twice daily versus placebo (Cheng et al., 2009). Patients receiving sorafenib had significantly better median overall survival (6.5 versus 4.2 months) and TTP (2.8 versus 1.4 months). The treated group in the Asian trial had a shorter survival duration than the control group in the SHARP trial (6.5 versus 7.9 months), despite the fact that both trials used the same entry criteria. Patients accrued to the Asian study were more ill at the start of therapy than those in the SHARP trial, with a generally worse performance status and more advanced stage of disease (Raoul et al., 2008). Preliminary data suggest that patients with hepatitis C virus (HCV) infection as the etiology of their cirrhosis may have a better response to sorafenib as compared to those with other etiologies of the HCC (Huitzel-Melendez et al., 2007; Bolondi et al., 2008). However, the available data are scant, and further study is needed to establish the influence of underlying

liver disease on sorafenib treatment responsiveness. With the advances in our understanding of the pathophysiology of this disease and the development of new biomarkers, we may be able to better identify patients who might benefit most from sorafenib treatment.

3.2 Sorafenib plus doxorubicin

The benefit of adding sorafenib to doxorubicin was studied in a phase II trial in which all patients received doxorubicin (60 mg/m² every 21 days), and they were randomly assigned to sorafenib 400 twice daily for a maximum of six cycles or placebo (Abou-Alfa et al., 2010). Combination therapy was associated with a similarly low objective response rate (4 versus 2 percent with doxorubicin alone), but a significantly longer time to tumor progression (6.4 versus 2.8 months) and median overall survival duration (13.7 versus 6.5 months). The side effect profile was not significantly worse with combined therapy.

The degree to which this improvement represents synergism between sorafenib and doxorubicin remains to be defined. Before this approach can be considered standard, this combination must be compared to sorafenib alone in a large-scale phase III trial, which is ongoing.

3.3 Sunitinib

Sunitinib is another orally active TKI that targets a variety of TKs in addition to VEGFR, including platelet-derived growth factor receptors (PDGFRs), KIT, RET, and FLT3. Antitumor activity is suggested by the following early observations:A phase II study included 37 patients with unresectable HCC who were treated with sunitinib (50 mg daily for four of every six weeks) and assessed by monthly CT scans (Faivre et al.,2009). There was one confirmed partial response, and 35 percent had stable disease for over three months.

3.4 Small molecule TK inhibitors

Small molecule TKI, erlotinib has shown some activity in phase II studies of advanced HCC patients with tumors expressing EGFR/HER1. Philip et al. treated 38 patients with advanced HCC, one half of whom had prior chemotherapy using 150 mg of erlotinib orally daily on 28-day cycles. Twelve patients out of 38 (32 percent) were progression free at six months while three had a radiographic response that lasted for two, 10 and 11 months respectively. (Philip et al., 2005). The median survival of the entire cohort was 13 months. A second trial included 40 patients with previously untreated unresectable HCC who received erlotinib 150 mg daily as monotherapy (Thomas et al., 2007). There were no objective responses, but 17 achieved stable disease with 16 weeks of continuous therapy. The median overall survival was 11 months. Additional studies with other receptor TKIs, both as monotherapy and in combination with cytotoxic chemotherapy are ongoing.

3.5 Bevacizumab

Bevacizumab, a monoclonal antibody against the VEGF, has been shown to be active in HCC. In one study involving 46 patients with locally advanced HCC single agent bevacizumab was given at 5 mg/kg or 10 mg/kg every two weeks.(Siegel et al.,2008) An objective response was documented in six (13 percent, one complete), and the median progression-free survival was 6.9 months. The most common grade 3 or 4 toxicities were

hypertension (15 percent), thrombosis (6 percent) and major bleeding (11 percent). A similar level of efficacy was seen in a second trial, reported in abstract form only (Malka et al., 2007). Using bevacizumab 5 to 10 mg/kg every 14 days, there were three partial responses and 13 disease stabilizations among 30 patients, and six had to discontinue therapy because of variceal bleeding.

3.6 Erlotinib plus bevacizumab

In a study of bevacizumab (10 mg/kg every two weeks) plus erlotinib (150 mg orally daily, continuously), was associated with a response rate of 25 percent and a stable disease rate of 37 percent. The median progression-free and overall survival durations were 9 and 15.6 months, respectively (Thomas et al.,2009). These results appear favorable compared with those reported in phase II and III trials of sorafenib as a single agent (median survival 6.5 to 14 months). Randomized trials are needed to confirm the superiority of erlotinib and bevacizumab over other systemic regimens.

3.7 Bevacizumab plus gemcitabine plus oxaliplatin

In a small phase II trial 30 patients received gemcitabine (1000 mg/m^2) followed by oxaliplatin (85 mg/m^2) on days 2 and 16, plus bevacizumab (10 mg/m^2 on day 1 of the first cycle and thereafter, on days 1 and 15 of each cycle) (Zhu et al., 2006). The objective response rate was 20 percent, the six-month progression-free survival rate was 48 percent, and median overall survival was 9.6 months. Whether any combination regimens are better than bevacizumab alone will require a randomized trial.

3.8 Cetuximab

Early results suggest activity for cetuximab in combination with GEMOX (Louafi et al., 2007). In a preliminary report of 44 patients who received gemcitabine 1000 mg/m^2 on day 1 and oxaliplatin 100 mg/m^2 on day 2 every 14 days, in combination with cetuximab (400 mg/m^2 initially, then 250 mg/m^2 weekly), there were eight partial responses, and the total disease control rate (partial response plus stable disease) was 65 percent. Treatment was well tolerated with only one grade 4 toxicity (thrombocytopenia) and no grade 5 toxicities. Grade 2 and 3 neurotoxicity occurred in 16 and 5 percent of patients, respectively.

4. Hormone therapy

4.1 Tamoxifen

HCC known to express hormonal receptors and the striking gender disparity observed in the incidence of hepatocellular carcinoma has suggested an important role of sex hormones in HCC pathogenesis. Though the studies began as early as in 1980s, the precise role of sex hormones and the significance of their receptors in HCC still remain poorly understood and perhaps contribute to current controversies about the potential use of hormonal therapy in HCC(Kalra M et al., 2008). Several prospective randomized trials and a systematic review of tamoxifen in patients with advanced HCC have failed to show a survival benefit or improved functional status (Castells et al., 1995; Chow et al., 2002; Nowak et al., 2004; Barbare et al., 2005). One possible reason for the lack of efficacy may be the presence of variant ERs in some of these tumors (Villa et al., 1996; Villa et al., 2001). Tamoxifen may also function as a potential inhibitor of p-glycoprotein, the MDR (multidrug resistance) gene

product, and this has led to trials of tamoxifen combined with various chemotherapeutic agents. Unfortunately, these studies have also failed to demonstrate any benefit for the addition of tamoxifen (Cheng et al.., 1996; Raderer et al., 1996).

4.2 Megestrol

Unlike tamoxifen there has been some modest benefit with the use of megestrol in some studies involving patients with HCC. In a study of 24 patients with advanced HCC who were randomly assigned to megestrol (160 mg daily) or supportive care only, median survival was significantly better with megestrol (18 versus 7 months) despite no objective responses(Farinati et al., 2001). In another study, one of 37 patients receiving megestrol (160 mg daily) for at least 60 days had a partial response, while two others had a significant decline in serum alpha-fetoprotein (AFP) levels (Chao et al., 1997).

4.3 Octreotide and lanreotide

In a review of four randomized controlled trials (three of which were high quality trials) published in 1998 or later with a total of 373 patients only one (126 patients) suggested that octreotide could improve survival and quality of life of HCC patients, whereas the other two(189 patients) suggested octreotide did not have survival benefit in HCC; moreover, none of the three trials indicated that octreotide has significant beneficial effect on tumor regression or decrease of tumor mass. Nonetheless, serious adverse effects were not reported in these included trials. In order to detect a realistic treatment advantage, further larger well-designed multicenter randomized trials will have to be conducted(Jia et al., 2010).

Lanreotide is a long acting somatostatin analog that is available in a depot formulation that has comparable efficacy to octreotide when injected intramuscularly two to three times per month. Although limited antitumor activity has been suggested in nonrandomized studies a randomized trial of lanreotide versus placebo in 272 patients with advanced HCC failed to show any advantage for drug treatment in terms of progression-free or overall survival, and treatment was associated with worse quality of life (Barbare et al., 2009).

5. Immunomodulatory/antiangiogenic therapy

5.1 Lenalidomide

Last but not he least, Lenalidomide, an immunomodulatory analog of thalidomide, an anti-angiogenic agent with inhibitiory effects on basic fibroblast growth factor (FGF) and vascular endothelial growth factor (VEGF) has shown promising and in some patients dramatic activity. FGF is an important growth factor in HCC. In a phase II study to determine the activity of lenalidomide in Second-line HCC therapy, patients with advanced HCC who progressed or were intolerant to sorafenib were treated with lenalidomide 25 mg orally days 1-21 of a 28 day cycle until disease progression or unacceptable toxicity. A preplanned interim analysis was undertaken when study enrollment reached 13 out of the total planned 40 patients. Of the first 13 patients, the median age was 66 years (44-86 years). Eight patients were Child-Pugh A, 3 patients were B, and 2 patients were C. Nine patients had extrahepatic disease. Five of 13 patients (38%) had a > 50% reduction in AFP including one patient with a reduction in AFP from 56,900 to 5 ng/mL. Two patients had radiographic partial responses including one patient with complete resolution of all areas of enhancement. Treatment was well tolerated with grade 3 neutropenia seen in 2 patients (Safran et al., 2010)

6. Active clinical trials in HCC

Clinical trials for patients with Advanced Hepatocellular Carcinoma (HCC) are listed below. The list of clinical trials includes treatment trials currently recruiting in the United States. Further information regarding each clinical trial can be reached at *www.canliv.org/Doctors--amp;-Researchers/Active-Clinical-Trials*

- Sorafenib and TRC105 in Hepatocellular Cancer
- A Study of LY2157299 in Patients With Hepatocellular Carcinoma
- Axitinib For The Treatment Of Advanced Hepatocellular Carcinoma
- A Study of Ramucirumab (IMC-1121B) Drug Product (DP) and Best Supportive Care (BSC) Versus Placebo and BSC as 2nd-Line Treatment in Patients With Hepatocellular Carcinoma After 1st-Line Therapy With Sorafenib
- A Study of the Effectiveness and Safety of AMG 386 and Sorafenib to Treat Advanced or Inoperable Hepatocellular Cancer
- Study of Bavituximab and Sorafenib In Patients With Advanced Liver Cancer
- Global Study Looking at the Combination of RAD001 Plus Best Supportive Care (BSC) and Placebo Plus BSC to Treat Patients With Advanced Hepatocellular Carcinoma.
- Efficacy and Tolerability of ABT-869 Versus Sorafenib in Advanced Hepatocellular Carcinoma (HCC)
- A Study of IMC-A12 in Combination With Sorafenib in Patients With Advanced Cancer of the Liver ABT-888 and Temozolomide for Liver Cancer
- A Randomized, Placebo-controlled, Double-blind Phase 2 Study With OSI-906 in Patients With Advanced HCC Bevacizumab and Erlotinib or Sorafenib as First-Line Therapy in Treating Patients With Advanced Liver Cancer

7. Conclusions

In this chapter we tried to summarize systemic therapy options for patients with advanced unresectable disease who are not candidates for locoregional therapy. This is a constantly evolving field. In general, efficacy with conventional cytotoxic chemotherapy has been modest at best, and the duration of benefit is limited. Although few randomized trials have been conducted, no single regimen seems to be superior and no drug or regimen has been unequivocally shown to improve survival. Newer data on the efficacy of molecularly targeted agents has been promising offering the potential for prolonged survival. Participation in ongoing clinical trials testing new therapeutic strategies is the best option for patients with advanced unresectable disease. For patients who are not eligible for a clinical trial or for whom protocol therapy is not available initial therapy with sorafenib 400 mg twice daily is the first line recommendation. To improve tolerability starting at 200 mg twice a day and increase the daily dose in 200 mg increments approximately every five days until the target dose is reached is a feasible option.

The efficacy of cytotoxic chemotherapy is at best modest in patients with HCC, and in general, the duration of benefit is limited. No single regimen has emerged as superior to any other, although few randomized trials have been conducted. Despite objective responses that are occasionally complete, median survival in all of these studies has been short (4.4 to 11.6 months), with the exception of those in which resection/transplantation is attempted after chemotherapy. There are insufficient data to routinely recommend any standard

regimen. Systemic chemotherapy may still be considered for patients whose tumors progress while on sorafenib and whose performance status and baseline liver function are sufficient to tolerate it. The side effect profile of any chemotherapy regimen should be considered carefully in patients with advanced liver disease and a short life expectancy. Cytotoxic therapy should be reserved for medically appropriate patients with adequate hepatic function and preferably administered within the context of a clinical trial. Reactivation of viral hepatitis may occur in patients with HCC who are undergoing intensive systemic chemotherapy, so it is important to monitor and maintain antiviral medications during treatment.

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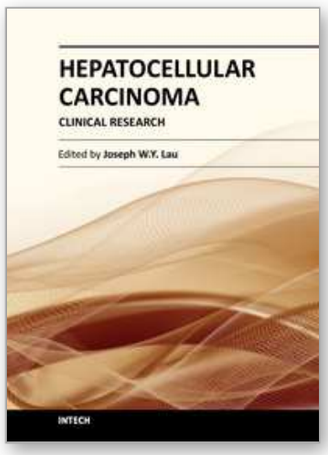

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This book covers the clinical aspects of hepatocellular carcinoma. This book is a compendium of papers written by experts from different parts of the world to present the most up-to-date knowledge on the clinical aspects of hepatocellular carcinoma. This book is divided into three sections: (I) Diagnosis / Differential Diagnosis; (II) Surgical Treatment; (III) Non-surgical Treatment. There are 19 chapters covering topics from novel diagnostic methods to hepatic lesions mimicking hepatocellular carcinoma, from laparoscopic liver resection to major hepatectomy without allogeneic blood transfusion, from molecular targeted therapy to transarterial radioembolization, and from local ablative therapy to regional therapy. This volume is an important contribution to the clinical management of patients with hepatocellular carcinoma. The intended readers of this book are clinicians who are interested in hepatocellular carcinoma, including hepatologists, liver surgeons, interventional and diagnostic radiologists, pathologists and epidemiologists. General surgeons, general physicians, trainees, hospital administrators, and instruments and drug manufacturers will also find this book useful as a reference.

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